REMARKS

In general, applicants' invention features a novel gene family, the members of which encode regulators that control the onset of acquired resistance responses in plants. This invention is based on applicants' discovery of a gene encoding a novel disease resistance protein characterized by the presence of ankyrin repeats, as well as their finding that the transformation of the cloned gene into plants conferred broad-spectrum disease resistance. Importantly, the invention provides for the genetic engineering of long-lasting, broad-spectrum resistance in crops.

Office Action

In the Office Action mailed on March 12, 2001, claims 1, 2, 4-13, 15-29, 36, and 40-42 were rejected under 35 U.S.C. § 112, first paragraph. Claims 10-13, 15-29, 36, and 40-42 were rejected under 35 U.S.C. § 112, second paragraph. Claims 1, 2, 4-13, 15-29, 36, and 40-42 were rejected as anticipated by or obvious in view of Ryals et al. (U.S. Pat. No. 6,091,004). Each of these rejections is addressed as follows.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected, under 35 U.S.C. § 112, first paragraph, on the basis that the disclosure in applicants' specification (1) fails to provide a written description of the claimed invention and (2) is not commensurate in scope with the claimed invention. For the following reasons, each of these rejections is respectfully traversed.

Written Description

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected, under 35 U.S.C. § 112, first paragraph, on the basis that the specification provides only a sequence for the *Arabidopsis NPR1* gene and therefore does not provide an adequate written description of the invention, as currently claimed. In rejecting the claims, the Examiner, in essence, asserts that (1) the "ankyrin motif is not a structural motif unique to the claimed genus of sequences involved in disease resistance," and (2) a "representative number of species of the claimed genus" has not been described. As support for this rejection, the Federal Circuit's opinion in *Univ. of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1387 (Fed. Cir. 1997) was cited.

Applicants respectfully traverse this rejection as their specification satisfies the written description requirement set forth by the case law and the U.S. Patent & Trademark Office's Written Description Guidelines (the "Guidelines").

The Guidelines, under the "Genus Analysis" decision tree, states:

> What is a representative number of species depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed. (Emphasis added.)

Given that applicants' specification describes the claimed class of acquired resistance genes and their shared, characteristic ankyrin repeats, this standard is satsified. On this point, the Examiner's attention is directed to applicants' specification, for example, at page 6 (line 12) and at page 8 (line 9), where it is

stated that an "acquired resistance polypeptide includes an ankyrin-repeat motif." Additionally, the specification, at page 43 (line 27) – page 44 (line 1) states:

> The cDNA sequence [NPR1] was analyzed using the BLAST sequence analysis program. This analysis revealed that the NPR1 protein shared significant homology with ankyrin, including the region identified as the ankyrin-repeat consensus.

Given its molecular role in disease resistance, the claimed family of disease-resistance polypeptides are readily distinguishable from unrelated ankyrin-repeat-containing polypeptides that have been described in the literature, which, to the best of applicants' knowledge, have not been shown to possess this property. Moreover, because acquired resistance plant defense responses are ubiquitous in the plant kingdom, and because applicants have demonstrated that an ankyrin-repeat-containing polypeptide controls the onset of such responses in *Arabidopsis*, it is entirely reasonable to assume that other plants possess and express such genes to regulate disease resistance. Based on applicants' description, one skilled in the art would immediately recognize that applicants' invention encompassed — not one gene — but a family of genes encoding ankyrin-repeat-containing, disease resistance polypeptides.

In a further analysis of the written description requirement, the Guidelines provide an example (Example 17), where the specification disclosed rat cDNA sequences only, but claimed a mammalian or human cDNA sequence. The written description requirement was held not to be satisfied in this case, because:

> . . .neither the specification nor the general knowledge of those skilled in the art provide evidence of <u>any partial structure</u> which would be expected to

> be common to the members of the genus. Moreover, there is post filing evidence that indicates that there is a lack of structural relationship between the rat insulin cDNA sequences and other mammalian insulin cDNA sequences. (Emphasis added.)

Thus, the implication is that had there been at least a partial structure common to members of the genus, or post-filing evidence of a structural relationship between the members of the genus, then the written description requirement would have been satisfied. The Guidelines, citing applicable case law, also state:

> A description of a genus of cDNAs may be achieved by means of recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1998). (Emphasis added.)

The facts of this case fall squarely with the Office's Written Description Guidelines. The present specification discloses that the claimed genus includes genes encoding polypeptides having an ankyrin repeat, a structural feature common to members of the genus. In addition, post-filing evidence, presented by Bougri et al.,[1] demonstrates that acquired resistance genes from wheat, corn, and rice share "significant sequence homology in the region of ankyrin repeats" with the *Arabidopsis* NPR1 acquired resistance gene, signifying that this structural feature is common to members of the genus. Thus, there can be no question that applicants were in possession of the claimed genus at the time their application was filed, that this genus does indeed include a family of ankyrin repeat disease

[1] See Bougri et al., Acquired Resistance Genes in Plants, WO 00/70069 (Exhibit 1), page 32 (lines 15-17) (Exhibit 1).

resistance proteins, and that one skilled in the art would recognize applicants' disclosure as a description of the invention defined by the present claims. As a result, applicants' specification clearly satisfies the written description requirement, as set forth by the case law, and applicants request reconsideration and withdrawal of this basis for the § 112 rejection.

Scope of Enablement

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected, under 35 U.S.C. § 112, first paragraph, on the basis that the teaching of applicants' specification is not commensurate in scope with the present claims. The rejection essentially turns on the assertion that it would require undue trial and error experimentation to identify genes that are structurally and functionally related to the disclosed isolated nucleic acid molecules encoding the NPR1 polypeptides.

Applicants submit that, contrary to this assertion, their specification clearly enables the subject matter presently claimed simply by providing applicants' newly identified *NPR1* sequence. In particular, given the teaching of the specification and the level of skill known in the art at the time the present application was filed, genes falling within the scope of applicants' claims could routinely be identified and isolated from a variety of plant sources using nothing more than standard techniques of molecular biology.

With respect to gene isolation methodologies, clear instructions for isolating other claimed nucleic acid molecules are provided in the specification under the heading "Isolation of Other Acquired Resistance Genes," at pages 50-52. There, applicants set

forth general guidance on the routine methods known at the time the application was filed for identifying the gene sequences required by the claims. These standard cloning methods described in the specification include: (1) the design and utilization of oligonucleotides for cloning acquired resistance gene sequences, (2) low- and high-stringency hybridization cloning methodologies, (3) library screening procedures, and (4) PCR-based amplification cloning strategies. Using such techniques, genes falling within the claims may be readily isolated, absent undue experimentation, from virtually any plant using applicants' *NPR1* sequence as a starting material.

In addition, once isolated, these gene sequences may be subjected to standard DNA sequencing to confirm their structural relatedness to the disclosed *NPR1* gene and its encoded ankyrin-repeat-containing polypeptide. If desired, publicly available sequence analysis software may be utilized for rapidly identifying the ankyrin-repeats. It cannot be disputed that all of the above methods are routinely used in the art of molecular biology and that all were well established at the time applicants filed their application.

In addition, as further evidence that genes encoding applicants' ankyrin repeat-containing, disease resistance polypeptides may be isolated using nothing more than standard techniques, the Examiner is directed to the present specification, for example, at pages 49-50. There, under the heading "Isolation of Solanaceous AR Genes," applicants demonstrate the successful and straightforward isolation of an *NPR1* homolog from tobacco. This homolog was identified by screening a cDNA library with a probe prepared from the full-length *Arabidopsis NPR1* cDNA. The isolated solanaceous acquired resistance gene, like the cruciferous *NPR1* gene, was found to encode an

ankyrin-containing polypeptide. In addition, the tobacco NPR1 homolog shows significant sequence identity to the *Arabidopsis* NPR1 gene product. Consistent with these results in tobacco are the results described in the present specification at page 52 (lines 4-15). There, results of an RNA blot experiment are described that demonstrate the existence of yet another *NPR1*-hybridizing RNA, in this case, in potato.

Such data strongly corroborate applicants' assertion that structurally related gene sequences falling within applicants' claimed invention exist, and that they may be identified and isolated from a variety of plant sources using applicants' *NPR1* sequence and standard techniques that are both described in the present specification and known in the art. There can be no question that the guidelines provided by the teachings of applicants' disclosure have been effective for such gene identification from at least two plants other than *Arabidopsis*, and a plant family other than crucifers, and there is no reason to believe that *NPR1* homologs cannot similarly be identified from any number of other sources.

With respect to the further issue of whether such genes would confer disease resistance, applicants again refer to the present specification. As taught, for example, at page 69 (lines 15-17), the ability of a structurally related gene to confer plant disease resistance is easily established using any of a variety of methods, including a straightforward, one-step screening technique. The specification makes clear that broad-spectrum pathogen resistance is readily obtained by expressing an acquired resistance transgene to initiate a plant defense response. Moreover, at pages 45-46, the specification demonstrates that overexpression of a *35S-NPR1* transgene in *Arabidopsis* conferred

resistance on the plant to bacterial and fungal pathogens. Accordingly, a skilled worker need only prepare transgenic plants overexpressing a gene found to be structurally related to *NPR1*, and then evaluate the plant's ability to combat a pathogen. Such a single-step screening approach cannot and does not constitute undue trial and error experimentation.

Finally, applicants note that the Examiner grounds the rejection on the assertion that there is no "definitive evidence demonstrating the existence of a structurally related DNA encoding a polypeptide comprising an ankyrin repeat motif." This assertion is incorrect. On this point, applicants again direct the Examiner's attention to Bougri's ankyrin repeat containing Npr homologs. In particular, applicants direct the Examiner's attention to Bougri, at page 52, where under the heading "Analysis of transgenic rice for enhanced resistance," Bougri states that "[t]ransgenic overexpression of *Nph1* and *Nph2-1*[2] Npr homologs promotes strong resistance against *M. grisea*." Here Bougri, after identifying the ankyrin repeat containing rice and wheat Npr homologs, respectively *Nph1* and *Nph2-1*, overexpressed the wheat and rice Npr homologs, independently, in rice. Overexpression of these Npr homologs resulted in lines of rice having resistance to fungal blast disease (see Bourgri, at page 52, lines 25-26).[3] Further confirming applicants' teaching, Bougri, at page 52 (lines 26-27), states that "these results suggest that both wheat and rice Npr homologs, when expressed in rice, enhance the SAR

[2] The *Nph1* and *Nph2-1* genes are described by Bougri (WO 00/70069; Exhibit 1) at page 8 (lines 15-22) as being *Npr1* homologs respectively from rice and wheat.

[3] Applicants point out that Bougri (WO 00/70069; Exhibit 1), at page 50 (lines 27-28), notes that one of the wheat Npr homologs, *Nph2-1*, "[did] not appear to promote disease resistance in [transgenic] wheat."

pathway." Thus, Bourgri not only corroborates that applicants' claimed acquired resistance gene family encodes polypeptides having an ankyrin repeat, but also corroborates that such proteins, when overexpressed in rice, confer enhanced disease resistance to a plant pathogen. Given this evidence, there is no scientific reason for doubting the existence of applicants' claimed gene family of disease resistance polypeptides.

Applicants also point out that, to sustain an enablement rejection, the Office has the initial burden to establish a reasonable basis to question the enabling nature of an applicant's specification. Thus, in a case in which the PTO questions the enablement of a claim, the CCPA, in *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367, 369 (CCPA 1971) has stated that:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support (emphasis added).

The MPEP (§ 2164.04, Eighth Edition, August 2001) further emphasizes the *Marzocchi* standard in stating that:

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure (emphasis added).

Applicants note that for all of the aforementioned reasons no scientific evidence currently made of record in this case establishes a basis for doubting the objective truth of the statements found in applicants' specification regarding enablement with respect to isolating genes falling within applicants' claims and determining whether such genes possess disease resistance properties. As is discussed above, applicants' statement that expression of an acquired resistance gene encoding a polypeptide possessing an ankyrin repeat confers pathogen resistance on host plants is in accordance with the evidence described in the present specification for the *NPR1* gene and the post-filing evidence of Bougri. Moreover, given the evidence described above, the Examiner has provided no evidence or reason for doubting applicants' statement that other genes having the structural features described by applicants would function similarly as disease resistance genes.

In conclusion, the facts in the present case compel withdrawal of the § 112, first paragraph enablement rejection, and applicants request reconsideration on this issue.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 10-13, 15-29, 36, and 40-42 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 10-12 were deemed indefinite in reciting the phrase "specifically hybridizes to" because the phrase is indefinite. Claims 10-12 that include this term have

been amended to state "hybridizes," as suggested by the Examiner in the final office action mailed March 12, 2001. The indefiniteness rejection may therefore be withdrawn.

Rejections under 35 U.S.C. §§ 102(e)/103

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected under 35 U.S.C. § 102(e) as anticipated by or obvious in view of Ryals (U.S. Patent No. 6,091,004; the "Ryals '004 patent"). Despite the fact that as of its earliest provisional priority date, June 21, 1996, Ryals provided no written description of a single acquired disease resistance gene, the Examiner asserts that the Ryals ATCC-deposited 100kb BAC-04 clone either anticipates or renders the claims obvious. This rejection may be withdrawn.

As an initial matter, applicants note that they disagree with the Office's current position on anticipation. Ryals does not anticipate applicants' claimed invention. As stated in previous correspondence, the Ryals priority document, provisional application no. 60/020,272, filed June 21, 1996, fails to disclose a DNA molecule free of other genes from the genome encoding an acquired resistance gene, as is claimed by applicants. In fact, Ryals fails to disclose any isolated plant resistance gene sequence. Absent such a sequence, Ryals cannot anticipate applicants' claimed invention, and the § 102(e) rejection may be withdrawn.

To expedite prosecution of this case, however, applicants submit herewith the Declaration of Dr. Xinnian Dong,[4] attesting to the fact that applicants had completed as

[4] Applicants note that Dr. Dong's 37 C.F.R. §1.131 declaration should not be considered unless it is determined that applicants are claiming an invention which is patentably distinct from that claimed in the Ryals '004 patent. *See* M.P.E.P (8th ed.) § 2308.01.

much as was disclosed in Ryals prior to May 8, 1996. Specifically, the Dong Declaration demonstrates that Dr. Dong, along with her co-inventors, had by that date determined that the *NPR1* gene resided on a yeast artificial chromosome ("YAC") clone designated "yUP19H6." In addition, prior to that date, the present inventors determined that three RFLP markers--m305, yUP21A4L, and g8020--were closely linked to the *NPR1* gene. Given that applicants possessed the yUP19H6 YAC clone and understood that this clone contained the *NPR1* gene prior to not only Ryals' provisional filing date, but also prior to the alleged ATCC deposit date of the BAC-04 clone, the Ryals '004 patent cannot be prior art to the claimed invention under 35 U.S.C. § 102(e), and the anticipation/obviousness rejection should be withdrawn.

Conclusion

Applicants submit that the claims are now in condition for allowance, which action is respectfully requested. If at least one of the pending claims in this application is found allowable and is claiming the same invention as at least one claim of the Ryals '004 patent, applicants respectfully request that the Examiner proceed to propose an interference.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 10 May 2002

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Version of Claims Showing Changes Made, Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

10. An isolated nucleic acid molecule that [specifically] hybridizes to a nucleic acid molecule comprising the genomic nucleic acid sequence of Fig. 4 (SEQ ID NO:1), wherein said isolated nucleic acid molecule encodes an acquired resistance polypeptide comprising an ankyrin repeat, said acquired resistance polypeptide conferring, on a plant expressing said polypeptide, resistance to a plant pathogen.

11. An isolated nucleic acid molecule that [specifically] hybridizes to a nucleic acid molecule comprising the cDNA of Fig. 5 (SEQ ID NO:2), wherein said isolated nucleic acid molecule encodes an acquired resistance polypeptide comprising an ankyrin repeat, said acquired resistance polypeptide conferring, on a plant expressing said polypeptide, resistance to a plant pathogen.

12. An isolated nucleic acid molecule that [specifically] hybridizes to a nucleic acid molecule comprising the DNA sequence of Fig. 7A (SEQ ID NO:13), wherein said isolated nucleic acid molecule encodes an acquired resistance polypeptide comprising an ankyrin repeat, said acquired resistance polypeptide conferring, on a plant expressing said polypeptide, resistance to a plant pathogen.